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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,272	12/19/2000	Charles Raymond Degenhardt	8371	6508

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THE PROCTER & GAMBLE COMPANY
INTELLECTUAL PROPERTY DIVISION
WINTON HILL TECHNICAL CENTER - BOX 161
6110 CENTER HILL AVENUE
CINCINNATI, OH 45224

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	7

DATE MAILED: 05/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/741,272	DEGENHARDT ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,9,11 and 18-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,9,11,18-23,25-27 and 29-31* is/are rejected.

7)☒ Claim(s) *24 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 3/25/02. Applicants have amended claims 2, 4, 5, 9, and 11. Applicants have canceled claims 1, 3, 6, 7, 8, 10, and 12-17. Claims 18-31 are new. There are nineteen claims pending and under consideration. Claims 2, 4, 5, 9, 11, and 18-24 are compound claims. Claims 25-28 are composition claim. Claims 29-31 are a use claims. This is the second action on the merits. The application concerns some 2-piperidinylcarbonyl-piperidines.

Election/Restrictions

2. Applicant's election with traverse of Group II in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Response to Amendments and Arguments

3. Applicants' replacement of claim 1 by claim 18 overcomes the improper Markush rejection made in point #6 of the previous office action. Applicants' amended title overcomes the objection made in point #7. Applicants' cancellation of claim 1 renders moot the indefiniteness rejection, regarding "active compound" made in point #9. Applicants' amendment defining what a heteroatom is, overcomes the indefiniteness rejection made in point #10. Applicants point to various preferred "substituents" on the variously claimed radicals and argue that

this is an art-recognized term. This is persuasive and the indefiniteness rejection made in point #11 is withdrawn. Applicants' amendment to claim 4, clarifying that the heterocyclic group is the piperidine, formed by the linking or R^2 and R^3, overcomes the indefiniteness rejection made in point #12. Applicants' deletion of C(O) as a possible group R^4 overcomes the anticipation rejections over Vicar (Collect. Czech. Chem. Commun.), Balaspiri (Acta Phys. Chem.), Kovacs (Pharmacol. Biochem. Behav.), Martin (Tetrahedron Lett), and Guzi (WO 00/37458) made in points #16-#20. Applicants' requirement that the piperidine ring, formed by the linking or R^2 and R^3, must be substituted overcomes the anticipation rejection over Sato ('239) made in point #22.

Claim Rejections - 35 USC § 112

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 2, 4, 5, 9, 11, 18-23, 25-27, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "about 10", "about 4", and "about 9" in claim 18 are indefinite. The ring A must contain a positive whole number of members.

Applicants cite a number of US patents, which contain such atomic descriptors in the claims, and argue that even indivisible numbers may be modified

by such terms. This is not persuasive for two reasons. Firstly, the indefiniteness remains despite what was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others. See *In re Margaroli,* 50 CCPA 1400, 318 F.2d 348, 138 USPQ 158 (1963); *In re Wright*, 45 CCPA 1005, 256 F.2d 583, 118 USPQ 287 (1958); *In re Launder*, 41 CCPA 887, 212 F.2d 603, 101 USPQ 391 (1954)".

Secondly, while the term "about" has been acceptable in claims dealing with continuous ranges like temperature in chemical process arts, the present claim language does not clearly set the metes and bounds of the claim since one cannot readily determine what is and what is not within the instant scope. Are ten atoms intended or something else? Applicants make no effort in their response to provide the answer. The U.S. Court of Appeals Federal Circuit wrote in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016 at 1030 "[t]he court found the "addition of the word 'about' seems to constitute an effort to recapture ... a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which

mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155[,000] might fit within that number," he had not "given a lot of direct considerations to that...."

5. New claims 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "and combinations thereof" is indefinite for two reasons. Firstly, since there are only two members of the group what the plural "combinations" imply? Secondly, lines 26-29, page 2 of the specification says that Applicants compounds treat multidrug resistance by inhibiting the two transport proteins P-glycoprotein and MRP1. If Applicants cannot treat multidrug resistance without inhibiting transport protein activity, what does combination mean? Presumably, one could inhibit transport protein activity

without treating multidrug resistance and that issue is addressed under 35 U.S.C. 112, first paragraph below. Combination means that both activities are done independently. If so how? This is a new rejection to claims first presented in Applicants last amendment.

6. Claims 2, 4, 5, 9, 11, 18-23, 25-27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrases "biohydrolyzable amide", "biohydrolyzable ester", and "biohydrolyzable imide" in claim 18 are unduly functional.

Applicants argue that synthesis of such compounds would be within the skill of the ordinary organic chemist. The Examiner aggress that if the structures of the products are known that it would be routine to make such amides, esters, and imides from the appropriate acids, amines etc. Since the structures of these "biohydrolyzable" compounds are uncertain, direction for their preparation must be even more unclear. Applicants further argue that it would be art-recognized which amides, esters, and imines would be "prodrugs" and "biohydrolyzable". With this, the Examiner does not agree. Applicants have not asserted that there is

any "prodrug" review of the same stature of Greene (protecting Groups), nor does the Examiner believe that any such text exists. Determining if a particular amide, ester, or imine is "biohydrolyzable" will involve undue experimentation.

According to the MPEP §2163 I. A. "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function." *In re Bell*, 26 USPQ2d 1529, *Fiers v. Revel*, 25 USPQ2d 1601 at 1605; *Eli Lilly*, 43 USPQ2d 1398 at 1405. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 *In re Ruschig*, 154 USPQ 118, *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481.

7. Claims 2, 4, 5, 9, 11, 18-23, 25-27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of the formula of claim 18 with R^5 = 5-quinolinyloxy, does not reasonably provide enablement for the myriad of hydrocarbon, heterogeneous, carbocyclic, heterocyclic, and heteroaromatic groups claimed for R^5. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims. Compounds made and tested represent the scope of claim 24, not claim 18. There is no reasonable basis for the assumption that the myriad of compounds embraced the present claim 18 will all share the same biological properties. The diverse claimed fused heteroaryl rings are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of cancer chemotherapy that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724.

Applicants argue that their claim language is no broader than their disclosure and that the skilled medicinal chemist would be able to prepare any of the claimed molecules containing all groups claimed for R^5. Applicants cite MPEP §2164.08 in support of their position. Presumably they refer to section (b) which reads "[h]owever, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)."

This is not persuasive because no rejection was made based on how to make the compounds or that the claims were broader than the disclosure. Rather the rejection was premised on the non-predictable nature of multi-drug resistance medicinal chemistry and the lack of ability of the skilled medicinal chemist to predict which groups claimed for R^5 would give active compounds and which would not. Describing an invention as broadly as it is claimed does not necessarily enable the skilled artisan to make or use the invention. Literal support for the claims was present *In re Surrey* 151 USPQ 724 previously cited. Finding that literal support for the claims in the chemical arts was not sufficient, the court relied heavily upon on an earlier decision *In re CAVALLITO AND GRAY*, 127 USPQ 202 at 205, which stated, "[t]he mere statement of an inventive concept, however, is not a sufficient basis for claiming it. Sufficient information must be given to enable those skilled in the art to practice the invention."

Regarding the enablement rejection made to claims 2, 4, 5, 9, 11, 18-23, 25-27, 29, and 30 in structure-sensitive arts, the MPEP says in §2164.03 "**Relationship of Predictability of the Art and the Enablement Requirement** The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA

1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention."

"The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)."

8. Claims 2, 4, 5, 9, 11, 18-23, 25-27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 lacks description.

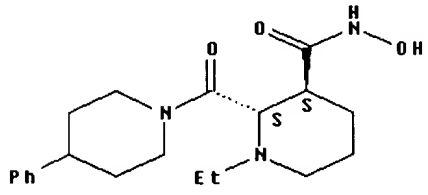
Nowhere in the specification is such a relationship linking the description between the two radicals described. The concept of linking the value of r to the specific divalent radical present as R^4 is not present. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts." Please also see the anticipation rejection over Xue (WO 99/65867) made below.

9. Claims 29-31 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating multidrug resistance, does not reasonably provide enablement for "inhibiting transport protein activity" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This claim would read on transport protein activity

inhibition in mammals with normal transport protein activity, in mammals with below normal transport protein activity, or in asymptomatic mammals with up-regulated transport protein activity. The specification fails to teach any benefit to be gained from such actions.

Claim Rejections - 35 USC § 102

10. Claims 2, 4, and 11 remain rejected and new claims 18, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Due (WO 99/65867). There are six compounds in this reference that anticipate Applicants compound claims, one of which is shown below. It has $R^5 = O_rR^6$, r = 0, R^6 = the hydrocarbon group methyl, t= 0, $R^4 = CH(R^1)$, R^1 = hydrogen, A = piperidine, w = 1, R^8 = N-hydroxy-3-carboxamide, x = 0, and NR^2R^3 = 4-phenyl-1-piperidinyl. The compound is described in the table on page 108 and is compound 75. Please also see claims 5 and 7 of this reference.



Applicants' proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 and discussed above excludes the art disclosed by

Xue (WO 99/65867). However, this proviso constitutes new matter and the rejection is maintained.

Allowable Subject Matter

11. Claims 24 and 28 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The specific compounds and compositions of these claims are not taught by Xue (WO 99/65867). No prodrugs are claimed and the compounds meet the enablement requirements discussed above in point #7.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In

no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
May 29, 2002